NSBRI Human Performance Factors, Sleep and Chronobiology Team Strategic Plan

5.0 HUMAN PERFORMANCE FACTORS, SLEEP & CHRONOBIOLOGY

Team Leader: Charles A. Czeisler, Ph.D., M.D.
Professor of Medicine, Harvard Medical School
Chief, Division of Sleep Medicine, Brigham and Women's Hospital
221 Longwood Avenue, Room 438A, Boston, MA 02115
Telephone: 617-732-4013; Fax: 617-732-4015
Email: caczeisler@rics.bwh.harvard.edu

Associate Team Leader: George C. Brainard, Ph.D.
Professor of Neurology, Thomas Jefferson University
Jefferson Medical College, Department of Neurology
1025 Walnut Street, Philadelphia, PA 19107
Telephone: 215-955-7644; Fax: 215-923-7588
Email: george.brainard@mail.tju.edu

5.1 INTRODUCTION

Sleep and circadian rhythm systems are fundamental regulatory processes of the nervous system and together comprise one of the most ubiquitous endogenous controls of human biobehavioral functions—everyone is internally programmed to sleep every night. The need for sleep is a homeostatic drive that occurs regardless of time of day, but the endogenous circadian pacemaker also modulates it. Conversely, the endogenous circadian pacemaker oscillates regardless of the need for sleep, although its promotion of wakefulness can be overwhelmed by elevated homeostatic sleep drive. These two powerful neurobiological systems interact continuously to control brain state (i.e., waking vs. sleep) and the intensity of state (e.g., alert vs. drowsy wakefulness). Sleep and circadian rhythmicity also temporally modulate a wide range of physiological functions (e.g., body temperature, cardiovascular activity, respiration, immune responses), hormonal functions (e.g., growth hormone, melatonin, cortisol, thyroid hormones), behavioral functions (e.g., movement, posture, reaction time), and cognitive functions (e.g., fatigue, alertness, vigilance, memory, cognitive throughput). No astronaut—no matter how much training, preparation, nutrition, psychosocial support, or environmental protection is provided—can avoid the daily control of physiology and performance by the homeostatic drive for sleep and the endogenous circadian timing system. Failure to take these two interactive neurobiological imperatives into account when planning human activities in space could have catastrophic consequences.

The success of human space missions depends on each astronaut remaining alert and vigilant while operating sophisticated equipment and following complex procedures. During exploration class space missions, the space environment affects a number of physiological systems critically involved in human performance, and it is vital to mission success to understand the biological limits of human performance under such conditions. It has been demonstrated that both acute gravitational changes and space flight disrupt circadian rhythms and reduce sleep. Since circadian disruption and sleep loss result in both physiological and performance deficits, this team is focused on these issues. In particular, the team is concerned with the following aspects of the space environment: weightlessness (microgravity), altered light-dark cycles and altered or reduced sleep/rest opportunities that may involve extended durations of

wakefulness. The primary thrust of this team's research program involves developing countermeasures for altered circadian organization, sleep disruption and cumulative sleep loss, and the associated neurobehavioral performance, metabolic and/or physical decrements occurring during exploration class missions.

The circadian pacemaker and the need for sleep have a sustained influence over many biomedical systems essential for maintaining astronaut physical condition, mental health, and performance capability. Dysfunction of sleep and circadian systems can adversely affect an organism's ability to respond to environmental challenges and has been linked to physiological and psychological disorders. This field of inquiry therefore has a high degree of relevance to a number of areas, such as cardiovascular and immune function, bone and muscle strength, neurovestibular physiology, nutritional needs, and behavioral and psychological health in space flight.

5.2   RISKS

The following risks in the Human Behavior and Performance Discipline Area of the Critical Path Roadmap have been identified:
- Human Performance Failure Because of Sleep and Circadian Rhythm Problems (19)
- Human Performance Failure Because Of Human System Interface Problems and Ineffective Habitat, Equipment, Design, Workload, or In-flight Information and Training Systems (19)

Risk number 19 includes both neurobehavioral performance failure as well as physiological performance failure due to sleep or circadian rhythm disturbances and is a very complex risk. For our research purposes, therefore, we have broken this risk down further into:
- Risk of Human Neurobehavioral or Physiological Performance Failure Due to Disruption of Circadian Phase, Amplitude, Period, or Entrainment During Space Exploration.
- Risk of Human Neurobehavioral or Physiological Performance Failure Due to Acute or Chronic Degradation of Sleep Quality or Quantity During Space Exploration

5.3   GOALS

The Human Performance Factors, Sleep and Chronobiology Team has the following goals for its program:

Risk-Based Goals

Goal 1: *Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration.*

Goal 2: *Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.*

Goal 3: *Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.*

Non Risk-Based Goals

Goal 4: *Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight.*

Goal 5: *Develop new methods for monitoring ambient and retinal light exposure (illuminance/photopic lux, broadband visible irradiance, and circadian effective illuminance/circadian lux) on board space shuttle and ISS during space flight and on planetary habitats.*

Goal 6: *Develop Earth-based applications of technologies for non-invasively monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance for industrial and medical use.*

Goal 7: *Develop Earth-based applications of high-fidelity mathematical models of performance based on circadian organization and sleep-wake history for industrial and medical use.*

Goal 8: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment.*

Goal 9: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to acute and chronic degradation of sleep quality or quantity.*

Goal 10: *Develop Earth-based applications of technologies developed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work.*

Goal 11: *Integrate research and analysis*

5.4   DESCRIPTION AND EVALUATION OF CURRENT PROGRAM

Current Research Program

The Human Performance Factors, Sleep and Chronobiology Team is focused on developing countermeasures for the sleep loss and circadian dysfunction and associated neurobehavioral performance decrements that occur during long-duration space flight.   The team research objectives are driven by the Critical Path Roadmap related to Human Performance Failure because of Sleep and Circadian Rhythm Problems. The current research program involves nine ground-based research projects. The strategy of the Human Performance Factors, Sleep and Chronobiology Team is to develop a synergistic interaction between research projects at the molecular, cellular, organism, and human levels, and to integrate predictive biomathematical modeling of the sleep and circadian systems.

In 2001, the HPFSC Team was substantially restructured. The current team is comprised of nine PIs, six of whom are new NSBRI investigators. Three of these six new NSBRI investigators are new to the space science community, a direct result of the recruitment efforts made within the science community. In order to achieve the goals listed above, the Human Performance Factors, Sleep and Chronobiology Team has identified the following five interrelated themes within this research area:

A. **Effects of long-duration space flight on sleep and/or circadian rhythmicity.** This theme addresses the impact of the conditions of long-duration space flight (microgravity, altered light intensity, spectrum and timing, loss of geophysical cues, isolation, altered physical activity, etc.) on neurobiologic, endocrinological, and behavioral mechanisms (molecular, cellular and organismic) that control sleep and circadian systems.

B. **Monitoring and assessment during space flight.** This theme deals with the development of methods for monitoring the status of sleep, sleep homeostasis and circadian organization and astronaut light exposure, as well as technologies that monitor ambient lighting conditions on space shuttle and ISS and assess and update the current functional status or performance capability of the individual.

C. **Countermeasures to optimize sleep and facilitate circadian adaptation in space and maintain optimal neurobehavioral performance and physical health**. The research program of this team will not only define the impact of the space environment on sleep and circadian rhythmicity and the effects of the sleep loss and circadian dysfunction on performance but also will develop methods to counter the adverse physiological and behavioral consequences of sleep loss and/or circadian dysfunction. These countermeasures may include behavioral, pharmacological, photic, environmental light or other adaptive approaches to maintain function and performance under the adverse conditions of long-duration space flight.

D. **Predictive modeling of performance based upon circadian organization and sleep homeostasis.** This theme is concerned with the development of mathematical models incorporating multiple model subsystems (e.g., circadian rhythmicity, sleep homeostasis, work-rest schedules, etc.) that: 1) predict individual and average human performance capability 2) predict the impact of countermeasures on performance, metabolic function or physical health and well-being; and 3) allow for schedule optimization.

E. **Effects of sleep loss and/or circadian dysfunction on neurobehavioral performance and/or physical health.** The focus of this theme is to identify the range of acute and chronic adverse effects that sleep loss, sleep disruption, and/or circadian dysfunction have on critical physiologic and performance parameters during long-duration space flight (e.g., metabolic functions, glucose tolerance, insulin resistance, neurophysiologic function, physiological alertness, vigilance, cognitive performance, mood/morale, problem solving and communication).

The initial strategic research program for the Human Performance Factors, Sleep and Chronobiology Team addresses the five research themes described above and is focused on developing countermeasures for the sleep loss and circadian dysfunction and associated neurobehavioral and physiological performance decrements that occur during long-duration space flight. The schematic of the circadian and homeostatic regulation of sleep and alertness and physiological functions shown in Diagram 5.1 illustrates the relationships between the nine current ground-based experiments that comprise the Team, with the principal targets of each project indicated. This diagram illustrates the interrelated nature of the projects, designed to fill critical gaps in knowledge that need to be filled in order to develop effective countermeasures for long-duration space flight. Each of the individual projects is summarized below and in Table 5.1, including which goal(s) are addressed and countermeasure targets.

Brainard et al.: *Optimizing Light Spectrum for Long Duration Space Flight*
The physiological changes caused by disturbed circadian rhythms and altered sleep-wake patterns can result in decrements in alertness, concentration, and performance. This project addresses these risk factors, which threaten the safety of personnel and the objectives of space missions as stated in Goals 1 and 3.
Countermeasure targets include:
1. Identification of the optimum spectrum for photic resetting of the circadian pacemaker;

2. Design specifications for space suit visors and the windows used in space vehicles and habitats; and
3. Engineering parameters for the ideal spectral distribution for illumination of general living quarters during space exploration.

Czeisler et al.: *Circadian Entrainment, Sleep-Wake Regulation & Performance during Space Flight*
The intent of this project is to develop countermeasures to facilitate adaptation of the human circadian pacemaker to the 24.65-h day length of Mars, which is outside the range of entrainment of the human circadian pacemaker given the weak synchronizing stimuli within the Martian habitat. This project applies to Goals 1 and 3.

The primary **countermeasure target** is to evaluate the efficacy of intermittent bright light pulses as a treatment to reduce the risk of the misalignment of circadian phase, sleep disruption, associated decrements in neurobehavioral performance and reduction in nocturnal growth hormone secretion experienced by individuals exposed to the 24.65h Martian day.

Dinges et al.: *Countermeasures to Neurobehavioral Deficits From Partial Sleep Loss*
Using a response surface experimental paradigm (RSM), this project seeks to reduce neurobehavioral deficits and fatigue due to inadequate sleep in astronauts by investigating how variations in sleep duration and its circadian placement relate to the return of performance per time invested in sleep. This project applies to Goal 2.

Countermeasure targets include determination of the amount of naptime necessary to compensate for interrupted nocturnal sleep periods for the prevention of cumulative sleepiness and performance deficits.

Fuller et al.: *Primate Circadian Rhythms in the Martian Environment*
This project is focused on the ability of the circadian time system to synchronize to the Martian photic (spectrum and period) by examining the effects of 1.0, 1.5 and 2.0G on the period of the circadian pacemaker. A G vs. period model will be developed to predict the effect of the 0.38 G Martian environment on the period of the circadian pacemaker. Long-term (4 months) physiological and behavioral responses will be examined.

Countermeasure targets include the use of timed bright light pulses on circadian entrainment. This program will develop a primate model to evaluate physiological and behavioral consequences of long-term exposure of males and females to altered lighting and gravitational environments. This project applies to Goals 1 and 3.

Jewett et al.: *Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure*
The intent of this project is to further develop and refine our mathematical dynamic stimulus processing model so that it can accurately predict the phase and amplitude of the human circadian system under any lighting system especially those which are in space. The mathematical Neurobehavioral Performance model validated against performance data collected will result in the development of a user-friendly Performance Simulation Software program. Validation of data collected from portable light measuring devices for input into the simulation software is ongoing. This project applies to Goals 1 through 4.

Countermeasure targets include the design of shift schedules to allow astronauts to receive available bright light at appropriate times for proper circadian alignment with their sleep/wake schedules.

Menaker et al.: *A Model of Circadian Disruption in the Space Environment*
This project proposes to evaluate the effects of "constant" conditions and shift work schedules on the maintenance of circadian rhythmicity when the central and peripheral structures are abnormally phased. The resulting abnormal circadian organization is "dysphasia." This project applies to Goal 1.

Countermeasure targets include an evaluation of meal timing, melatonin administration, forced exercise, and short pulses of complete darkness as a treatment to reduce the risk of circadian dysphasia.

Morin et al.: *Circadian and Vestibular Relationships*
This project seeks to determine the route by which a correlate of the non-photic stimulus, i.e., locomotion, might gain access to the circadian rhythm system and shift rhythm phase. It has also opened the possibility that the vestibular system is a specific route by which sensory information related to head movement might gain access to the circadian system. This project applies to Goal 1.

Countermeasure targets include an evaluation of a non-locomotor, non-photic three-dimensional motion stimulus to activate functionally the vestibular and circadian systems, laying the groundwork for the future development of novel approaches for the treatment of space motion sickness and for resetting circadian phase.

Tosini et al.: *Long-Term Exposure to Dim Light Desynchronizes the Circadian System of Rats*
The goal of this project is to understand the mechanisms responsible for the desynchronization of circadian rhythm in locomotion and the enzymes responsible for the production of melatonin. Investigating the effect that internal desynchronization has on the immune response and motor and cognitive performances. This project applies to Goal 2.

Countermeasure targets include an evaluation of the use of melatonin as a pharmacological agent to counteract desynchronization of the circadian rhythms.

Turek et al.: *Animal Model for Sleep Loss and Circadian Disruption*
This project will focus on determining the effects of 12 hours of imposed wakefulness on circadian rhythms, sleep-wake cycles, neurobehavioral and motor performance measures during normal active and inactive periods. This project applies to Goals 1 and 2.

Countermeasure targets include both treatment with exercise, or with either physiological or pharmacological doses of melatonin to reduce the effects of circadian disruption and sleep loss as well as alleviating the adverse effects associated with work at different times of day.

Achieving Non Risk-Based Goals

Goal 4: *Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight.*
To achieve this goal, current studies are being conducted to assess the potential of using the Actiwatch-L (a wrist-worn light and actigraphy recording device already approved for space flight) to monitor sleep and light exposure of individual crewmembers while in space. This device could replace more extensive polysomnography devices used in more recent studies of sleep in space. Studies are also underway that compare the wrist-level Actiwatch-L light recordings with eye-level light measurements. However, development of a physically separate light recorder that is placed at another part of the body may be required for sufficient accuracy of crew member's light exposure. Work is progressing on the use of the

Actiwatch-L measurements as inputs to a mathematical model that can then predict the level of sleep homeostasis, phase of circadian rhythmicity and relative neurobehavioral performance levels.

Goal 5: *Develop new methods for monitoring ambient and retinal light exposure (illuminance/ photopic lux, broadband visible irradiance, and circadian effective illuminance/circadian lux) on board space shuttle and ISS during space flight and on planetary habitats.*

For measurement of retinal light exposure in space, please see Goal 4 above. For ambient light exposure, wall-mounted ambient light recording devices have been tested aboard the Space Shuttle in the Neurolab flight. The team's current studies will help determine the circadian effective illuminance and irradiance levels, and then these recording devices can be refined to measure circadian-activating light levels more precisely.

Goal 6: *Develop Earth-based applications of technologies for non-invasively monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance for industrial and medical use.*

The polysomnography device that was developed for the recording of sleep in space in the Neurolabb Shuttle flight has become a useful, wire-free device for recording polysomnography in lab-based and home-based basic science and clinical studies. This technology has the advantage of being appropriate for use when ambulatory and is straightforward enough for a trained person to apply to themselves.

The use of salivary melatonin as a marker of circadian phase has been applied in both space and on Earth and is a technology that allows the validation of experimental and modeling results in field studies in which plasma melatonin measurements would not be possible.

Mathematical models that are developed to predict neurobehavioral performance in space are also being used to determine appropriate shift scheduling, light exposure, sleep timing, and countermeasure applications for shift workers, pilots, military and medical personnel, and transportation workers who also face the challenges of restricted sleep and circadian misalignment here on Earth. Neurobehavioral test batteries that are developed for these projects are useful for the validation of mathematical models in field and laboratory studies as well.

Goal 7: *Develop Earth-based applications of high-fidelity mathematical models of performance based on circadian organization and sleep-wake history for industrial and medical use.*

The mathematical models of performance that are being developed in this project can be applied to any Earth-based situation in which it would be helpful to know the effects of a sleep/wake schedule and a light exposure pattern on resulting neurobehavioral performance (e.g., shift workers, pilots, military and medical personnel, and transportation workers). Therefore, the mathematical models developed here have been programmed into user-friendly simulation software that can be used by anyone to predict neurobehavioral performance given light exposure levels and sleep/wake history. This software is updated with model revisions and user-interface improvements on a regular basis.

Goal 8: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment.*

The studies conducted here improve our understanding of the effects of light on the human circadian system and the role that the circadian system plays in neurobehavioral performance. These findings are incorporated into our mathematical models on an ongoing basis. This allows us to then determine the best light schedule and intensities to reduce the risk of performance failure by appropriately aligning the

circadian system with the work/rest schedule. This technology is already currently in use in transportation, military and industrial settings here on Earth.

Goal 9: *Develop Earth-based application so technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to acute a chronic degradation of sleep quality or quantity.*
Our projects will help determine the amount and timing of sleep that best allows people to work extended and/or misaligned shifts with the least risk of performance failure. These findings will also be incorporated into the mathematical model being developed here. The model can then be used to help schedule rest/nap/sleep times so that they are the most effective in improving performance levels.

Goal 10: *Develop Earth-based applications to technologies developed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work.*
Studies investigating the effects of extended duration work schedules in these projects allow us to determine the best timing of countermeasures (light exposure, naps, melatonin, etc.) to improve performance. The neurobehavioral performance model can be used to select, and eventually optimize, these work schedules to enhance performance. These findings are completely applicable to any extended duration work schedules used here on Earth.

Goal 11: *Integrate research and analysis*
Our goal is to integrate research within the Human Performance Factors, Sleep and Chronobiology Team, with other teams, and with work being done by Team investigators not directly supported by NSBRI. See a summary of our activities in Table 5.2.

Diagram 5.1. Description of Current (2001) Program for Human Performance Factors, Sleep and Chronobiology. This diagram illustrates the relationships between the different physiological systems investigated by the different projects on the team. Illustrated are the influence of the retinal light exposure on the human circadian clock (circle with the oscillator symbol ~) and the influence on the sleep-wake state (S/W), and their effect on a number of physiological variables (melatonin, temperature, etc.). A combined influence of the circadian clock and sleep-wake is exerted on neurobehavioral variables (sleep-wake propensity, alertness, etc.). The sleep-wake state influence is illustrated via the intermediary of the sleep homeostat (SH), and sleep inertia (SI). The global influence of factors associated to Space Flight (micro gravity, isolation, etc.) on the sleep and circadian systems is also represented. The interaction of the Vestibular Nucleus (VN) and its output pathways with the circadian pacemaker is being investigated by one project.
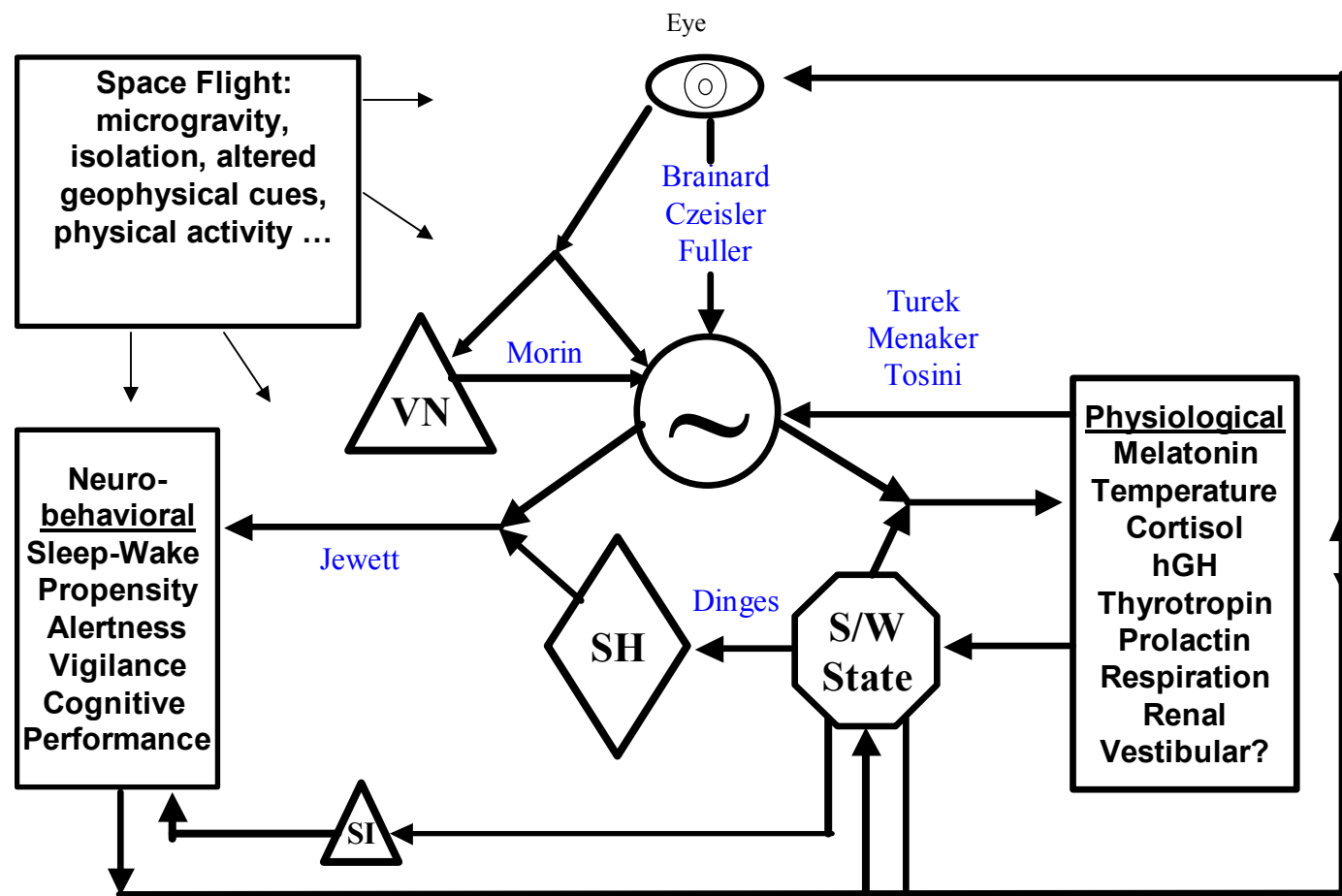
5.5   OBJECTIVES AND STRATEGIC ACTIVITIES

The objectives underlying each goal are presented below along with strategic activities that will be used to achieve the goals and objectives. Table 5.3 provides a timeline for the completion of these activities.

Risk-Based Goals

Goal 1: *Reduce the risk of human performance failure due to disruption of circadian phase, amplitude, period, or entrainment.*

Objective 1A: Assess risk and target level of acceptable risk
- Complete projects that characterize and quantify neurobehavioral performance decrements associated with circadian misalignment (Czeisler, Dinges, Jewett projects)
- Complete projects that quantify the impact of chronic circadian disruption on recovery sleep, circadian adjustment and/or neurobehavioral performance (Turek, Menaker and Tosini projects)

Objective 1B: Determine mechanisms
- Complete projects that investigate the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function in humans (Dinges project)
- Complete projects that fit stochastic and deterministic models to low-amplitude human temperature data to select lower- vs. higher-order models of human circadian amplitude recovery (Jewett project)
- Complete projects that determine the performance levels of desynchronized animals how desynchronized organisms respond to infections (Tosini project)
- Complete projects that validate refined circadian amplitude recovery dynamics of human light model (Jewett project)
- Complete projects that investigate the relationship between the degree of circadian disruption and the resulting impairment to neurobehavioral performance in mice (Turek project)

Objective 1C: Develop countermeasures
- Complete projects that test commercially available head-mounted light devices for circadian efficacy (Jewett, Brainard, Czeisler projects)
- Complete projects that test if bright light pulses facilitate entrainment to Martian day (Fuller project)
- Complete projects that determine the efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars (Czeisler project)
- Complete projects that determine the efficacy of intermittent bright light pulses of different intensities and/or wavelengths on circadian entrainment to non-24-hour work-rest schedules (Czeisler project)
- Complete projects that test pharmacological countermeasures (melatonin) to reduce the risk of internal desynchronization (Tosini project)
- Complete projects that apply knowledge gained with animal model to humans using measures of cognitive performance and physiological well-being to assess effectiveness (Menaker project)

- Complete projects that incorporate refined light model into circadian component of neurobehavioral performance model and predict neurobehavioral performance in human phase shifting experiments (Jewett project)
- Complete projects that test neurobehavioral model predictions against circadian and performance data collected under field conditions (Jewett project)
- Complete projects that test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic circadian disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that test if access to a wheel during rest periods (exercise) reduces the impact of chronic circadian disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that determine what duration of exercise optimally reduces the impact of chronic circadian disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that test pharmacological wake-promoting counter-measures (caffeine, modafinil) to reduce the risk of neurobehavioral performance failure due to circadian disruption (Czeisler allied projects)
- Initiate project that integrates into biomathematical model the impact of wake- and sleep-promoting therapeutics (pharmacological or behavioral) on neurobehavioral performance in the presence of circadian misalignment
- Initiate projects that ground test the efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic circadian disruption in humans
- Initiate projects that ground test the efficacy of pharmacological (e.g., melatonin), nutritional, environmental (e.g., light or dark pulses) or behavioral (e.g., exercise) circadian countermeasures designed to maintain internal synchrony of circadian oscillators in diverse organ systems in humans
- Initiate project to conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep
- Initiate project to conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic circadian disruption
- Initiate project to conduct projects that implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment

Goal 2: *Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality and quantity.*

Objective 2A: Assess risk and target level of acceptable risk
- Complete projects to characterize and quantify neurobehavioral performance decrements associated with sleep restriction and disruption (Czeisler, Dinges, Jewett projects)
- Complete projects that quantify the impact of chronic sleep restriction/disruption on recovery sleep and circadian adjustment (Turek, Dinges projects)

Objective 2B: Determine mechanisms
- Complete projects that determine the nature of neurobehavioral and physiological changes induced by chronic sleep restriction at different circadian phases (Dinges project)
- Complete projects that test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases (Dinges project)
- Complete projects that investigate the relationship between the degree of sleep disruption and the resulting impairment to neurobehavioral performance in mice (Turek project)

Objective 2C: Develop countermeasures
- Complete projects that develop and test candidate sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Dinges Project)
- Complete projects that test optimal sleep-wake schedules to minimize chronic neurobehavioral and physiological deficits at all circadian phases (Dinges project)
- Complete projects that test neurobehavioral model predictions against circadian and performance data collected under field conditions (Jewett project)
- Complete projects that test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic sleep restriction/ disruption on performance and recovery sleep in mice (Turek project)
- Complete project that tests if access to a wheel during rest periods (exercise) reduces the impact of chronic sleep restriction/disruption on performance and recovery sleep in mice (Turek project)
- Complete project that determines what duration of exercise optimally reduces the impact of chronic sleep restriction/disruption on performance and recovery sleep in mice (Turek project)
- Complete projects that test pharmacological wake-promoting counter-measures (caffeine, modafinil) to reduce the risk of neurobehavioral performance failure due to sleep loss (Czeisler allied projects)
- Complete projects that ground test the efficacy of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of microgravity on sleep in humans
- Initiate projects that integrate into biomathematical models the impact of wake- and sleep-promoting therapeutics (pharmacological or behavioral) on neurobehavioral performance in the presence of sleep restriction/disruption
- Initiate project to ground test the efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction in humans
- Initiate project to conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of microgravity on sleep
- Initiate project to conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction
- Initiate project that implements a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to sleep loss

Goal 3: *Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution*

Objective 3A: Assess risk and target level of acceptable risk
- Complete projects that describe disrupting effects of shifting schedules of light, food availability and exercise on phase relationships among circadian oscillators in brain and peripheral organs (Menaker project)
- Complete projects that characterize the effect of long-term exposure to constant conditions on the circadian system (Tosini project)
- Characterize and quantify the presumptive vestibular-circadian system anatomical connection (Morin project)
- Complete projects that determine how desynchronized organisms respond to infections (Tosini project)
- Initiate project to develop lighting monitoring system for inside of space shuttle and ISS
- Initiate projects that identify the effect of an altered circadian environment on the well being of the organisms

Objective 3B: Determine mechanisms
- Complete projects that develop human melatonin fluence-response curves below 440 nm and above 600 nm (Brainard project)
- Complete projects that quantify role of pupil dilation in circadian photic transduction in humans and that develop melatonin action spectrum in humans with freely reactive pupils (Brainard project)
- Complete projects that determine how desynchronized organisms respond to infections (Tosini project)
- Complete projects that describe disrupting effects of constant light on phase relationships among circadian oscillators in brain and peripheral organs (Menaker project)
- Complete projects that describe disrupting effects of shifting schedules of light, food availability and exercise on phase relationships among circadian oscillators in brain and peripheral organs (Menaker project)
- Complete projects that test entrainment to Martian day-length and both ambient and habitat lighting (Czeisler project)
- Complete projects that identify promising pharmacological countermeasures to reduce the risk of desynchronization (Menaker, Tosini, Turek projects)
- Complete project that determines effect of altered gravity on circadian period in primates (Fuller project)
- Complete projects that test human melatonin response to simulated ISS, EVA and martian light environments (Brainard, Fuller and Czeisler projects)
- Complete projects that determine functional activation of the vestibular and circadian systems by an optokinectic nystagmus stimulus (Morin project)

Objective 3C: Develop countermeasures
- Complete projects that determine the functional activation of the vestibular and circadian systems by a non-locomotor, non-photic, vestibular activating stimulus (Morin project)
- Complete first test of human circadian phase-shifting with selected monochromatic wavelengths (Brainard and Czeisler project)

- Complete projects that ameliorate disruptive effects of constant light and shifting schedules using pulses of bright light, darkness, melatonin and applying regularized feeding and work schedules (Menaker project)
- Initiate projects that develop and ground test light sources that optimally stimulate human circadian responses and light sources that specifically do not stimulate human circadian responses
- Initiate projects that develop and ground test window and visor prototypes for optimal human circadian stimulation and prototypes that minimize human circadian responses
- Initiate projects that integrate current ISS and shuttle lighting with new light sources and window systems

Non Risk-Based Goals

Goal 4: *Develop new methods for monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neurobehavioral performance during space flight.*
- Complete projects that assess the potential of using the Actiwatch-L (a wrist-worn light and actigraphy recording device already approved for space flight) to monitor sleep and light exposure of individual crew members while in space
- Complete projects that compare the wrist-level Actiwatch-L light recordings with eye-level light measurements
- Complete projects that use of the Actiwatch-L measurements as inputs to a mathematical model that can then predict the level of sleep homeostasis, phase of circadian rhythmicity and relative neurobehavioral performance levels
- Initiate projects that develop non-invasive electroencephalographic, electrooculographic and/or electromyographic monitoring techniques for recording the timing of the sleep-wake cycle during space flight
- Initiate projects that develop and evaluate new methods for monitoring sleep-wake fitness for duty during space flight
- Initiate projects that develop and evaluate new methods to monitor neurobehavioral performance during space flight without interfering with the operational demands of space flight
- Initiate projects that develop and evaluate new non-invasive methods for assessing circadian phase during space flight
- Initiate projects that develop and evaluate new non-invasive methods for assessing homeostatic sleep need during space flight

Goal 5: *Develop new methods for monitoring ambient and retinal light exposure (illuminance/photopic lux, broadband visible irradiance, and circadian effective illuminance/circadian lux) on board space shuttle and ISS during space flight and on planetary habitats.*
- Complete projects that analyze the data from the wall-mounted ambient light recording devices that have been tested aboard the Space Shuttle in the Neurolab flight
- Complete projects that determine the circadian effective illuminance and irradiance levels
- Initiate projects that refine these recording devices to measure circadian-activating light levels more precisely on board space shuttle and ISS during space flight and on planetary habitats

Goal 6: *Develop Earth-based applications of technologies for non-invasively monitoring the status of sleep, sleep homeostasis, circadian rhythmicity and neuro-behavioral performance for industrial and medical use.*

- Complete projects that develop neurobehavioral test for the validation of mathematical models in field and laboratory studies as well.
- Initiate projects that improve the polysomnography device that was developed for the recording of sleep in space in the Neurolab Shuttle flight
- Initiate projects that refine and develop current and new markers of circadian phase to be applied on Earth
- Initiate projects that develop non-invasive electroencephalographic, electrooculographic and/or electromyographic monitoring techniques for recording the timing of the sleep-wake cycle for industrial and medical use
- Initiate projects that develop and evaluate new methods for monitoring sleep-wake fitness for duty for industrial and medical use
- Initiate projects that develop and evaluate new methods to monitor neurobehavioral performance for industrial and medical use
- Initiate projects that develop and evaluate new non-invasive methods for assessing homeostatic sleep need for industrial and medical use

Goal 7: *Develop Earth-based applications of high-fidelity mathematical models of performance based on circadian organization and sleep-wake history for industrial and medical use.*

- Complete projects that refine mathematical models to predict neurobehavioral performance in space
- Complete projects that refine mathematical models to determine appropriate shift scheduling, light exposure, sleep timing, and countermeasure applications for shift workers, pilots, military and medical personnel, and transportation workers
- Complete projects that develop a user-friendly simulation software that can be used by anyone to predict neurobehavioral performance given light exposure levels and sleep/wake history
- Initiate projects that incorporate high-fidelity mathematical models of performance based on circadian organization and sleep-wake history into personal monitoring and display devices for industrial and medical use.

Goal 8: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment.*

- Complete projects to improve our understanding of the effects of light on the human circadian system, and the role that the circadian system plays in neurobehavioral performance.
- Complete projects that incorporate our findings into mathematical models to determine the best light schedule and intensities to reduce the risk of performance failure by appropriately aligning the circadian system with the work/rest schedule
- Initiate projects that produce technologies for medical and industrial use designed to reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase amplitude, period or entrainment

Goal 9: *Develop Earth-based applications of technologies developed to reduce the risk of human neurobehavioral or physiological performance failure due to acute a chronic degradation of sleep quality or quantity.*
- Complete projects to determine the amount and timing of sleep that best allows people to work extended and/or misaligned shifts with the least risk of performance failure
- Complete projects that incorporate our findings into the mathematical model to help schedule rest/nap/sleep times so that they are the most effective in improving performance levels
- Initiate projects that produce technologies for medical and industrial use designed to reduce the risk of human neurobehavioral or physiological performance failure due to acute chronic degradation of sleep quality or quantity.

Goal 10: *Develop Earth-based applications of technologies developed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work.*
- Complete projects that investigate the effects of extended duration work schedules to determine the best timing of countermeasures (light exposure, naps, melatonin, etc.) to improve performance
- Initiate projects that produce technologies for medical and industrial use designed to reduce the risk of neurobehavioral or physiological performance failure due to extended duration work schedules (e.g., on-call schedules used in medical training, nuclear power plant shutdowns, military operations) or night shift work

Goal 11: *Integrate research and analysis*
Objective 11A: Integrate research within the Human Performance Factor, Sleep and Chronobiology Team
- Continue current integration efforts among team PIs, and co-investigators.
Objective 11B: Integrate research with other teams
- Continue to build collaborative links between the Team projects and projects on other teams, especially other teams with a focus on Sleep and Circadian Physiology
- Coordinate with Neurobehavioral and Psychosocial Factors Team regarding the effects of sleep loss and circadian displacement, and countermeasures for these factors on cognition, mood and social interaction.
- Coordinate with the Neurovestibular Adaptation Team regarding the effects of space motion sickness and countermeasures for it on circadian entrainment
- Coordinate with the Nutrition and Rehabilitation Team regarding the potential for effects of chronic partial sleep loss on carbohydrate metabolism
- Coordinate with the Smart Medical Systems Team regarding the potential for neuroimaging to enhance objective detection of neurobehavioral dysfunction due to sleep loss during space flight.
Objective 11C: Integrate research being done by Team investigators with their other, related research projects that are not directly supported by NSBRI.
- Most of the investigators on the Human Performance Factor, Sleep and Chronobiology Team are conducting other research projects related to human performance factors, sleep and chronobiology that are supported by other federal and non-Federal agencies (Air Force, Department of Defense, NIH, NSF, NASA, etc.). We plan to integrate the results of that allied research with the results of their NSBRI

projects to facilitate the development of countermeasures for exploration class missions.

5.6   SUMMARY

The success of human space flight depends on astronauts remaining alert while operating highly complex, state-of-the-art equipment. A crucial factor of mission success is that crewmembers do not get enough sleep. The loss of 24-hour day/light cycle, weightlessness, a confined environment and work demands make sleep difficult in space. Astronauts sleep only six hours each night, on average. Exploration crews will have to switch their "body clock" from the Earth day to the day/night cycle of another planet. These factors may lead to cumulative sleep loss, increased risk of accidents and possible mission failure. The Human Performance Factors, Sleep and Chronobiology Team is focused on developing countermeasures to reduce human mistakes and optimize neurobehavioral and physiological performance during exploration class space missions.

National Space Biomedical Research Institute
HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 5.1. Project Research Activities

PI/Project	Risk(s) Addressed	Countermeasure Target	Experimental System	Phase 1 Activities: Focused Mechanistic Research	Phase 2 Activities: Preliminary Countermeasure Development Research	Phase 3 Activities: Mature Countermeasure Development Research
BRAINARD/Optimizing Light Spectrum for Long Duration Space Flight	Goals 1, 3	Optimum light spectral distribution	Healthy male and female human subjects	Develop melatonin fluence-response curves below 440 nm and above 600 nm in human subjects & develop action spectrum between 400 and 700 nm in subjects with dil./undilated pupils	Optimum light spectral character for maintaining or adjusting circadian phase & sleep-wake cycle. Preliminary test of monochromatic stimuli for phase shifting human circadian rhythms	Assist in designing a novel light panel for circadian stimulation. Assist in developing protocols for comparing head mounted light therapy devices
CZEISLER/Circadian Entraining, Sleep-Wake Regulation & Performance During Space Flight	Goals 1, 2	Intermittent bright light pulses	Healthy male and female human subjects scheduled to non-24-hour day lengths in an environment shielded from periodic, 24-h time cues	Quantification of intrinsic period and the limits of entrainment of the human circadian pacemaker & investigating the effects of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function	Preliminary evaluation of the efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars	Full-scale clinical trial of age and gender matched astronaut surrogates living for extended durations on a non-24-hour work schedule while exposed to intermittent bright light at the most effective wavelength
DINGES/Countermeasures to Neurobehavioral Deficits from Partial Sleep Loss	Goals 1, 2, 3	Naps and split sleep schedules	Healthy male and female human subjects	Track neurobehavioral performance deficits associated with chronic sleep restriction & examine sleep efficiency and architecture (restricted sleep periods at diff. circadian phases)	Develop response surface map paradigms to further understand the interaction between sleep duration, sleep-wake placement and neurobehavioral functioning	Development of optimal sleep-wake schedules (including main and supplementary sleep episodes) to ensure maintenance of high level neurobehavioral functioning

Note:
Goal 1: Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration.
Goal 2: Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration. **Goal 3:** Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.

FULLER/Primate Circadian Rhythms in the Martian Environment	Goals 1, 2	Bright light pulses	Rhesus monkeys as human surrogates. Long-duration studies in large-diameter Centrifuge with controlled lighting period, intensity and spectra.	Determine the effect of altered gravity on primate circadian rhythms, principally the endogenous clock period.	Enhance entrainment response to low light (ISS, Martian habitat), reddish light (Mars), and non-24 hour schedules by means of exposure to light pulses. Studies will address timing and efficacy of bright light exposure.	Projected application of bright light pulses to prevent loss of circadian entrainment, sleep and rhythm disturbances, and performance decrements.
JEWETT/Mathematical Model for Scheduled Light Exposure: Circadian/Performance Countermeasure	Performance decrement due to circadian misalignment and/or sleep restriction/disruption	Design of rest/work and sleep/wake and countermeasure delivery schedules to improve neurobehavioral performance	Previously collected human data;	Determine the nature of amplitude recovery dynamics of human circadian system.	Design shift and sleep schedules for proper circadian alignment. Validate refined circadian amplitude dynamics of light model.	Incorporate refined light model into circadian components of neurobehavioral performance model and predict the performance in human phase shifting.
MENAKER/ A Model of Circadian Disruption in the Space Environment	Goals 1,2	Coupling between multiple circadian oscillators	Transgenic rat incorporating a circadian luciferase reporter gene	Description of system disintegration under simulated space flight conditions	Repair system disintegration with timed application of light, food and melatonin	Transfer working countermeasures to humans
MORIN/Circadian and Vestibular Relationships	Goals 1,2	Anatomical & functional issues linking the vestibular & circadian systems	Anatomical tract tracing using retro and anterograde transport labels Study of brain regions for stimuli responses known to alter vestibular functions Phase shifts in circadian rhythms	Understanding the basic anatomical & functional pathways linking vestibular & circadian systems	N/A	N/A
TOSINI/Long-term Exposure to Dim Light Desynchronizes the Circadian System of Rats	Goals 1,2	Coupling between central and peripheral oscillators	Measuring expression of gene in peripheral tissues	Identification of the effects on the circadian system of prolonged exposure to constant conditions	Use of melatonin as synchronizing agent	

| TUREK/Animal Model for Sleep Loss and Circadian Disruption | Goals 1, 2 | Exogenous melatonin administration and exercise | Mice | To determine changes to sleep (architecture, duration and efficiency) and neurobehavioral performance associated with periods of imposed wakefulness at different circadian times | Testing of the effectiveness of countermeasures (melatonin, exercise) using a mouse model | N/A |

Note: Goal 1: Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space exploration.
Goal 2: Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.
Goal 3: Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.

HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 5.2. Integration Activities

	Brainard	Czeisler	Dinges	Fuller	Jewett	Menaker	Morin	Turek	Tosini
Internal Communication	Monthly team telecon, NSBRI January Retreat, informal discussions. Discussions with JSC staff: general lighting & and window design	Telecon and informal discussions with other team members	Czeisler et al, Jewett et al, Kosslyn et al, Lieberman et al	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members Czeisler et al, Dinges et al, Brainard et. al	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members	Telecon and informal discussions with other team members
Integrated Experiment Development	Dr. Fuller and Peter Smith: lighting specifications for simulated Martian environment for current primate studies and future animal and human studies. Dr. Jewett: developing protocols for comparing head mounted light therapy devices	Dr. Dinges: standardize neurobehavioral assessment. Dr. Fuller: coordination of primate-human models. Dr. Jewett: use of biomathematical model predictions re. intermittent bright light cm. Dr. Brainard: spectral sensitivity of circadian phase resetting.	Neurobehavioral performance assessment Neurobehavioral performance assessment	Dr. Brainard: develop a specification for simulated Martian ambient lighting, test apparatus, and document spectrum. Potential integrated experiment facility, with animal centrifuges and both rodent and primate habitats	Testing and validation of light emitting devices as potential countermeasures to circadian misalignment; Testi accuracy of wrist-we actigraphy/light collecting devices a potential use for inp to neurobehavioral models.	N/A	N/A	N/A	N/A
Sample Sharing	Accessed head mounted light stimulation systems from BioBrite Inc. and Leon Lack, MD, for Dr. Jewett's efficacy tests	Neurobehavioral and entrainment data with Jewett et al	Neurobehavioral data/ Jewett et al	N/A	Czeisler et al, Dinges et al	N/A	N/A	N/A	N/A

Synergistic Studies of Opportunity	Preliminary test of monochromatic stimuli for phase shifting human circadian rhythms with Drs. Czeisler and Lockley	The results of our growth hormone measures will be shared with the Muscle and Bone Teams, given the potential impact of the hypothesized chronic reduction in sleep-related growth hormone secretion on maintenance of muscle and bone function	Neurobehavioral performance testing during chronic sleep restriction and circadian displacement (stressful condition)/ Dinges et al (Neurobehavioral and Psychosocial) Circadian adjustment during chronic sleep restriction/ Czeisler et al (Sleep and Chronobiology)	We are currently exploring interest in both the rhesus model and hypergravity	Analyzing the output of actigraphy and light exposure data collected from crew members on Space Shuttle Missions for accuracy and for use as input data for our neurobehavioral models.	N/A	N/A	N/A	N/A
Development of Computer Model of Integrated Human Function	N/A	Contributing neurobehavioral and entrainment data for biomathematical model development (Jewett et al/ Sleep and Chronobiology) with ultimate goal of integrating performance model into model of Integrated Human Function	Contributing neurobehavioral data for biomathematical model development (Jewett et al/ Sleep and Chronobiology) with ultimate goal of integrating performance model into model of Integrated Human Function	Our findings should help define parameters of circadian response to gravity in combination with altered lighting environments.	Development and validation of refined model the effects of light on human circadian system. Refinement and validation of mathematical model of human Neurobehavioral Performance	N/A	N/A	N/A	N/A

National Space Biomedical Research Institute

HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 5.3a. Achieving Goal 1: Reduce the risk of human neurobehavioral or physiological performance failure due to disruption of circadian phase, amplitude, period, or entrainment during space.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research													
• Quantify neurobehavioral performance decrements associated with circadian misalignment and/or sleep restriction/disruption (Goals 1 and 2) • Observation of a presumptive vestibular-circadian system anatomical connection	▓												
• Identify the effect of an altered circadian environment on the well being of the organisms (Goals 1 and 3) • Characterize the effect of long-term exposure to constant conditions on the circadian system (Goals 1 and 3)		▓	▓	▓									
• Quantify the impact of chronic circadian disruption and/or sleep restriction/disruption on recovery sleep, circadian adjustment and neurobehavioral performance in different strains of mice (x2) entrained to different light levels (low, medium and high intensity) (Goals 1 and 2)		▓	▓	▓									
Phase 1: Focused Mechanistic Research													
• Fit stochastic and deterministic models to low-amplitude human temperature data to select lower- vs. higher-order models of human circadian amplitude recovery • Describe disrupting effects of constant light on phase relationships among circadian oscillators in brain and peripheral organs		▓	▓										
• Investigate the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function (Goals 1 and 2) • Determine how desynchronized organisms respond to infections (Goals 1 and 2) • Determine the performance levels of desynchronized animals (Goals 1 and 2)		▓	▓	▓									
• Develop human melatonin fluence-response curves below 440 nm and above 600 nm (Goals 1 and 3) • Quantify role of pupil dilation in circadian photic transduction in humans • Develop melatonin action spectrum in humans with freely reactive pupils • Establish the anatomy of connectivity between the circadian rhythm system and the vestibular system		▓	▓	▓									

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
• Investigate the relationship between the degree of sleep and/or circadian disruption and the resulting impairment to neurobehavioral performance in mice (Goals 1 and 2)			▓	▓									
• Describe disrupting effects of shifting schedules of light, food availability and exercise on phase relationships among circadian oscillators in brain and peripheral organs			▓	▓									
• Determine functional activation of the vestibular and circadian systems by an optokinectic nystagmus stimulus			▓	▓	▓								
• Identify promising pharmacological countermeasures to reduce the risk of desynchronization • Determine the effects of transients following phase shifts on neurobehavioral performance and sleep (Goals 1 and 2)				▓	▓	▓							
Phase 2: Preliminary Countermeasure Development Research	░	░	░	░	░	░	░	░					
• Test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases (Goals 1 and 2)	▓	▓	▓	▓	▓								
• Determine the functional activation of the vestibular and circadian systems by a non-locomotor, non-photic, vestibular activating stimulus		▓	▓	▓									
• Efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars (Goals a and 3)		▓	▓	▓									
• Validate refined circadian amplitude recovery dynamics of light model Ameliorate disruptive effects of constant light and shifting schedules using pulses of bright light, darkness, melatonin and applying regularized feeding and work schedules			▓	▓									
• Test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2) • Test if access to a wheel during rest periods (exercise) reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2) • Determine what duration of exercise optimally reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2) • Incorporate refined light model into circadian component of neurobehavioral performance model and predict neurobehavioral performance in human phase shifting experiments (Goals 1 and 2)				▓	▓								
• Test pharmacological countermeasures (melatonin) to reduce the risk of internal desynchronization (Goals 1 and 2)					▓	▓	▓	▓					
• Test human circadian phase-shifting with selected monochromatic wavelengths					▓	▓	▓	▓					

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 3: Mature Countermeasure Development Research				░	░	░	░	░	░	░	░		
• Determine minimum information required for tailoring neurobehavioral performance model to an individual crew member • Determine accuracy limits of neurobehavioral performance model • Develop a brief neurobehavioral test battery for immediate in-flight validation and calibration of performance model predictions				■	■	■	■						
• Efficacy of intermittent bright light pulses of different intensities and/or wavelengths on circadian entrainment to non-24-hour work-rest schedules (Goals 1 and 3)					■	■	■						
• Develop optimization techniques to generate sleep-wake schedules that minimize chronic neurobehavioral and physiological deficits due to circadian misalignment and sleep disruption (Goals 1, 2 and 3)					■	■	■						
• Apply knowledge gained with animal model to humans using measures of cognitive performance and physiological well-being to assess effectiveness								■	■	■	■		
• Ground test efficacy of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep in humans (Goals 1 and 2) • Ground test efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption in humans (Goals 1 and 2) • Ground test efficacy of pharmacological (e.g., melatonin), nutritional, environmental (e.g., light or dark pulses) or behavioral (e.g., exercise) circadian countermeasures designed to maintain internal synchrony of circadian oscillators in diverse organ systems in humans								■	■	■	■		
Phase 4: Countermeasure Evaluation & Validation							░	░	░	░	░	░	░
• Test neurobehavioral model predictions against circadian and performance data collected under field conditions								■	■	■	■		
• Validate that optimized sleep-wake schedules do minimize neurobehavioral and physiological deficits as predicted by neurobehavioral performance model (Goals 1 and 2)								■	■	■	■		
• Conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep (Goals 1 and 2) • Conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption (Goals 1 and 2)												■	■ >>>

Phase 5: Operational Implementation of Countermeasure Strategy														
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1,2 and 3)														>>>

National Space Biomedical Research Institute

HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 3b. Achieving Goal 2: Reduce the risk of human neurobehavioral or physiological performance failure due to acute or chronic degradation of sleep quality or quantity during space exploration.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research	▨	▨	▨	▨									
• Quantify neurobehavioral performance decrements associated with circadian misalignment and/or sleep restriction/disruption (Goals 1 and 2)	■												
• Determine the nature of neurobehavioral and physiological changes induced by chronic sleep restriction at different circadian phases	■	■	■	■									
• Quantify the impact of chronic circadian disruption and/or sleep restriction/disruption on recovery sleep, circadian adjustment and neurobehavioral performance in different strains of mice (x2) entrained to different light levels (low, medium and high intensity) (Goals 1 and 2)		■	■	■									
Phase 1: Focused Mechanistic Research		▨	▨	▨									
• Investigate the effect of circadian misalignment on sleep, neurobehavioral performance and neuroendocrine function (Goals 1 and 2)		■	■	■									
• Determine how desynchronized organisms respond to infections (Goals 1 and 2)		■	■	■									
• Determine the performance levels of desynchronized animals (Goals 1 and 2)		■	■	■									
• Investigate the relationship between the degree of sleep and/or circadian disruption and the resulting impairment to neurobehavioral performance in mice (Goals 1 and 2)			■	■									
Phase 2: Preliminary Countermeasure Development Research	▨	▨	▨	▨	▨	▨	▨	▨	▨	▨			
• Test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases (Goals 1 and 2)	■	■	■	■	■								
• Test if the administration of exogenous melatonin at either physiological or pharmacological levels at the beginning of the period of imposed wakefulness attenuates the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2)				■	■								
• Test if access to a wheel during rest periods (exercise) reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2)				■	■								
• Determine what duration of exercise optimally reduces the impact of chronic circadian disruption and/or sleep restriction/disruption on performance and recovery sleep in mice (Goals 1 and 2)				■	■								

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
• Test pharmacological countermeasures (melatonin) to reduce the risk of internal desynchronization (Goals 1 and 2)					█	█	█	█					
• Test pharmacological wake-promoting countermeasures (caffeine, modafinil) to reduce the risk of neurobehavioral performance failure due to sleep loss • Incorporate separate long-term effects of partial chronic sleep deprivation into mathematical models of neurobehavioral performance (Goals 1 and 2)					█	█	█	█					
• Integrate into biomathematical model the impact of wake- and sleep-promoting therapeutics (pharmacological or behavioral) on neurobehavioral performance in the presence of circadian misalignment and/or sleep restriction/disruption (Goals 1 and 2)									█	█	█		
Phase 3: Mature Countermeasure Development Research								▒	▒	▒	▒		
• Determine minimum information required for tailoring neurobehavioral performance model to an individual crew member • Determine accuracy limits of neurobehavioral performance model • Develop a brief neurobehavioral test battery for immediate in-flight validation and calibration of performance model predictions				█	█	█	█						
• Develop optimization techniques to generate sleep-wake schedules that minimize chronic neurobehavioral and physiological deficits due to circadian misalignment and sleep disruption (Goals 1, 2 and 3)					█	█	█	█					
• Ground test efficacy of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep in humans (Goals 1 and 2) • Ground test efficacy of pharmacological (e.g., caffeine, modafinil) or behavioral (e.g., exercise) wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption in humans (Goals 1 and 2)								█	█	█	█		
Phase 4: Countermeasure Evaluation & Validation								▒	▒	▒	▒	▒	▒
• Validate that optimized sleep-wake schedules do minimize neurobehavioral and physiological deficits as predicted by neurobehavioral performance model (Goals 1 and 2)								█	█	█	█		
• Conduct in-flight clinical trial of pharmacological sleep-promoting countermeasures to mitigate the adverse effects of circadian disruption and microgravity on sleep (Goals 1 and 2) • Conduct in-flight clinical trial of pharmacological wake-promoting countermeasures to mitigate the adverse effects of chronic sleep restriction and circadian disruption (Goals 1 and 2)												█	█ >>>

Phase 5: Operational Implementation of Countermeasure Strategy														
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1, 2 and 3)														>>>
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1 and 2)														>>>

HUMAN PERFORMANCE FACTORS, SLEEP AND CHRONOBIOLOGY PROGRAM

Table 3c. Achieving Goal 3: Reduce the risk of human neurobehavioral or physiological performance failure due to habitat design, equipment design or workload distribution during space exploration.

Countermeasure Development Phases	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 0: Observational & Phenomenological Research		░	░	░									
• Identify the effect of an altered circadian environment on the well being of the organisms (Goals 1 and 3) • Characterize the effect of long-term exposure to constant conditions on the circadian system (Goals 1 and 3)		█	█	█									
Phase 1: Focused Mechanistic Research		░	░	░	░								
• Develop human melatonin fluence-response curves below 440 nm and above 600 nm (Goals 1 and 3)		█	█	█	█								
• Determine effect of altered gravity on circadian period • Test entrainment to Martian day-length and ambient lighting • Test entrainment to Martian day-length and habitat lighting			█	█	█								
Phase 2: Preliminary Countermeasure Development Research	░	░	░	░	░	░	░	░					
• Test the impact of split sleep-wake schedules on chronic sleep deficits at different circadian phases	█	█	█	█	█								
• Determine the functional activation of the vestibular and circadian systems by a non-locomotor, non-photic, vestibular activating stimulus		█	█	█	█								
• Efficacy of intermittent bright light pulses on circadian entrainment to non-24-hour work-rest schedules, as required on Mars)(Goals 1 and 3)		█	█	█									
• Test commercially available head-mounted light devices for circadian efficacy			█	█	█								
• Develop lighting monitoring and actigraphy measurement system for individual crew members inside of space shuttle and ISS					█	█	█	█					
• Test human circadian phase-shifting with selected monochromatic wavelengths • Test human melatonin response to simulated ISS, EVA and lunar light environments						█	█	█					

Countermeasure Development Phases (cont'd)	Pre 2001	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Phase 3: Mature Countermeasure Development Research						░	░	░	░	░	░		
• Efficacy of intermittent bright light pulses of different intensities and/or wavelengths on circadian entrainment to non-24-hour work-rest schedules (Goals 1 and 3)						▓	▓	▓	▓				
• Validate lighting monitoring and actigraphy measurement system for individual crew members inside of space shuttle and ISS							▓	▓	▓	▓			
• Develop optimization techniques to generate sleep-wake schedules that minimize chronic neurobehavioral and physiological deficits due to circadian misalignment and sleep disruption (Goals 1, 2 and 3)					▓	▓	▓	▓	▓	▓			
• Develop light sources that optimally stimulate human circadian responses • Develop light sources that specifically do not stimulate human circadian responses • Develop window and visor prototypes for optimal human circadian stimulation • Develop window and visor prototypes that minimize human circadian responses								▓	▓	▓	▓		
Phase 4: Countermeasure Evaluation & Validation								░	░	░	░	░	░
• Ground test lights that optimally stimulate human circadian responses • Ground test lights that specifically do not stimulate human circadian responses • Ground test window and visor prototypes for optimal human circadian stimulation • Ground test window and visor prototypes that minimize human circadian response								▓	▓	▓	▓		
Phase 5: Operational Implementation of Countermeasure Strategy											░	░	░
• Integrate current ISS and shuttle lighting with new light sources and window systems (2010-2015) • Ground test integration of ISS lighting with new light sources and window systems (2012-2015) • Flight test integration of ISS lighting with new light sources, window systems											▓	▓	▓ >>>
• Implement a biomathematical model-based system in which countermeasures are deployed only when needed to reduce the risk of human neurobehavioral or physiological performance failure due to circadian misalignment or sleep loss (Goals 1, 2 and 3)													▓ >>>